Columbia University
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DEPARTMENT OF ZOÖLOGY

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Dr. Joshua Lederberg
Department of Genetics
University of Wisconsin
Madison 6, Wisconsin

Dear Josh:

Peg Lieb is interested in a post-doctorate fellowship for next year, and one of the people we naturally thought of her associating with was you. She has recently heard from Max Delbruck that she would be most welcome in his laboratories, and she would like to work there. I think you could do for her every bit what Max can, but since it seems an uncertain thing at Wisconsin, I believe she should aim at Cal. Tech. Max knows Peg--a fact which, combined with his willingness to have her, should convey the notion that she's not bad. In fact, she's quite bright. A little quick and a little demanding, but industrious enough to turn out ok.

Max thought she might like to work on the rate of formation of recombinants, a problem into which I think you will agree Tom Nelson has at least gotten his incisors. When Max hears of Tom's results he may feel somewhat more kindly towards your work. What the hell was bothering Harriett? Such reactionaries! Ah well, I suppose devil's advocates have a real place.

My own problems have been dissolving a bit more rapidly recently. I do not have the answer to the one on the discontinuous distribution of h^+ mutants. I have never been able to convince myself that the distribution is multi-modal and still want to test it against the theoretical one.

For this reason, I have written Coulson regarding his solution to the L.D. equation but have not had a response.

In somewhat better shape are several other jobs. Population equilibrium is pretty certainly accounted for by mutation rates and a changing selection pressure. We have been able to do more than calculate selection pressure at equilibrium by introducing a marked h^+ at this frequency and measuring its rate of disappearance (tracer technique). The measurement confirms the calculation (a 0.02% change in frequency of h^+'s per generation) and we are now using the same technique for other h^+ frequencies. In the meanwhile, I have been able to calculate that $s = 1/h^+$ frequency by a consideration of the rate of increase of h^+ through serial transfer to equilibrium.

At very low frequencies s turns out to be about 0.6. Such a selection allows an increase of h^+ bacteria (including those arising by mutation) which is operationally indistinguishable from that observed by the fractionation of liquid cultures and the use of the Posson formulation. So much for the logarithmic increase of h^+'s in an h- culture--we had already ruled out by other experiments the effect of one mutation on others.

We used the fractionation technique to avoid any influence of agar on the frequency of h^+ colonies. But it turned out our agar was not at fault. Adapted colonies do continue to appear on agar even when they cannot be accounted for by an increase in h- number. Indeed, stationary phase adaptations occur in liquid cultures, even after 7 days, with no increase in h-. By the use of variance analysis we have been able to show that these

adaptations are not due to the eventual growth of slow h^+ mutants which appeared during growth of the culture before it passed into the stationary phase. Now we are attempting to measure cell turnover during that phase by the use of marked bacteria. But our biggest problem is to decide whether we are simply observing release from phenotypic lag of the sort Evelyn Witkin thinks she is dealing with in her ribonucleate experiments. If mutations do occur in the stationary phase, it would be very worthwhile knowing, for the system would be ideal for the study of induced mutation.

Enough babble--

Sincerely yours,

Francis J. Ryan

FJR:LF